

and other study drug patients needed to receive the contents of two vials. To avoid bias in the trial, two different placebos were used, one with a small volume and the other with a larger volume, where the volumes corresponded to those of the study drug.

The end-result was that any physician administering a large volume would not likely be capable of guessing if the large volume dose contained placebo or study drug. Bevacizumab or placebo was administered intravenously and concurrently with chemotherapy every 3 weeks on day 1.

Patients in all four arms of the trial received cisplatin and gemcitabine (CG). Cisplatin was administered on day 1, and gemcitabine was administered on days 1 and 8, of each 21-day cycle. Drug administration was continued for 6 cycles. Regarding the two placebo groups, Reck et al. (76) stated that, “[p]atients assigned to high- and low-dose placebo were pooled into one placebo group for all analyses.”

Another example of using two different placebos, each corresponding to a lower dose and higher dose of study drug, comes from the example of cladribine for treating multiple sclerosis (77).

The following provides two situations where a double dummy design can be used. In all cases, the double dummy design is a technique for retaining the blind when administering supplies in a clinical trial, when the two treatments cannot be made identical (78).

The first design, which is from an example from the ICH Guidelines (79) involves a 2-arm study where the first arm receives a study drug and the second arm receives another drug, that is, an active control drug (this study design does not involve any placebo group):

- **Arm A.** All subjects in arm A receive a round pill that is the active control drug plus a flat pill that is the placebo.
- **Arm B.** All subjects in arm B receive a flat pill that is the study drug plus a round pill that is the placebo.

The second design, also shown below, is a 4-arm study, where two arms receive only drugs, and where the remaining two arms receive only placebo:

- **Arm A.** Round pill study drug.
- **Arm B.** Round pill placebo.
- **Arm C.** Flat pill active control drug.
- **Arm D.** Flat pill placebo.

⁷⁶ Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAIL. *J Clin Oncol*. 2009;27:1227–1234.

⁷⁷ Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *New Engl J Med*. 2010;362:416–426.

⁷⁸ ICH Harmonised Tripartite Guideline Statistical Principles for Clinical Trials E9. Feb. 1998 (46 pages).

⁷⁹ ICH Harmonised Tripartite Guideline Statistical Principles for Clinical Trials E9. Feb. 1998 (46 pages).